SECOND GENERATION GRP94-SELECTIVE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application No. 62/550,292, filed on Aug. 25, 2017, the entire disclosure of which is herein incorporated by reference for any and all purposes.

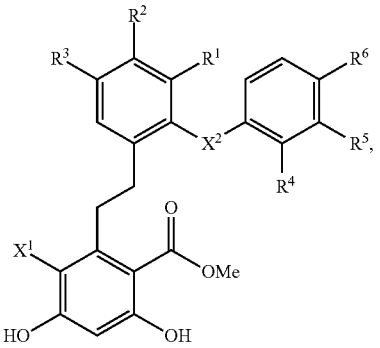
U.S. GOVERNMENT RIGHTS

[0002] This invention was made with government support under EY024232 and EY021205 awarded by the National Institutes of Health. The government has certain rights in the invention.

SUMMARY

[0003] In an aspect, a compound of Formula I is provided

(I)



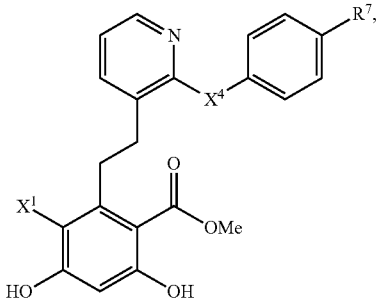
or a pharmaceutically acceptable salt thereof, wherein

X^1 is Cl or F;

[0004] X^2 is CH_2, O, S, or NH;
R^1, R^2, R^4, R^5, and R^6 are each independently H, alkoxy, hydroxyl, thiol, or halo, and
R^3 is H, alkoxy, amino, hydroxyl, thiol, or halo.

[0005] In an aspect, provided is a compound of Formula III

(III)



or a pharmaceutically acceptable salt thereof, wherein

X^3 is Cl or F;

[0006] X^4 is CH_2, O, S, or NH; and
R^7 is alkoxy, hydroxyl, thiol, or halo.

[0007] In another aspect, the present technology also provides compositions (e.g., pharmaceutical compositions) any of one of the embodiments of the compounds disclosed herein (or a pharmaceutically acceptable salt of any thereof) disclosed herein and a pharmaceutically acceptable carrier. The pharmaceutical composition may be for treating metastatic cancer and may include a pharmaceutically acceptable excipient. The pharmaceutical composition may be for treating glaucoma and may include a pharmaceutically acceptable excipient.

[0008] In a related aspect, a method for inhibiting cell motility of a cancer cell is provided, the method comprising contacting the cancer cell with a compound of any embodiment disclosed herein.

[0009] In a related aspect, a method of treating a patient or animal suffering from metastatic cancer is provided, the method comprising administration of an effective amount of a compound of any embodiment disclosed herein to the patient or animal suffering from the metastatic cancer.

[0010] In a related aspect, a method of inhibiting death of a cell exhibiting mutant myocilin is provided, the method comprising contacting the cell with a compound of any embodiment disclosed herein.

[0011] In a related aspect, a method of treating a patient or animal suffering from glaucoma is provided, the method comprising administration of an effective amount of a compound of any embodiment disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIG. **1**: Representative images of a wound healing scratch assay in different cancer cell lines after 24 h treatment with methyl 3-chloro-2-(2-(4-fluorobenzyl)phenethyl)-4,6-dihydroxybenzoate ("compound 30") of the present technology or vehicle (0.25% final concentration of DMSO), according to the working examples. Scale bar=100 μm.

[0013] FIG. **2**: Western blot analysis for the Grp94-dependent client protein Integrin α2, the cytosolic Hsp90-dependent client protein Akt, Hsp70, and loading control actin after treatment with 30 at indicated concentrations for 24 h (0.1% DMSO final concentration), according to the working examples. D=DMSO, G=geldanamycin, a natural product, pan-Hsp90 inhibitor (0.5 μM).

[0014] FIG. **3**: Representative images of a wound healing scratch assay in MDA-MB-231 cancer cell line after 24 h treatment with 30 or vehicle (0.25% final concentration of DMSO), according to the working examples. Scale bar=100 μm.

[0015] FIG. **4**: Representative images of a wound healing scratch assay in PC3-MM2 cancer cell line after 24 h treatment with 30 or vehicle (0.25% final concentration of DMSO), according to the working examples. Scale bar=100 μm.

[0016] FIG. **5**: Representative images of a wound healing scratch assay in SK-MEL-28 cancer cell line after 24 h treatment with 30 or vehicle (0.25% final concentration of DMSO), according to the working examples. Scale bar=100 μm.

[0017] FIG. **6**: Representative images of a wound healing scratch assay in A549 cancer cell line after 24 h treatment with 30 or vehicle (0.25% final concentration of DMSO), according to the working examples. Scale bar=100 μm.